Use of Coumarin Anticoagulants and Cerebral Microbleeds in the General Population

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Background and Purpose—It remains undetermined whether the use of coumarin anticoagulants associates with cerebral microbleeds in the general population. We investigated whether (1) coumarin use relates to higher prevalence and incidence of microbleeds, (2) microbleeds are more frequent in people with higher maximum international normalized ratios (INRs), and (3) among coumarin users, variability in INR associates with microbleed presence.

Methods—From the population-based Rotterdam Study, 4945 participants aged ≥45 years were included in the cross-sectional analysis, and 3069 participants had follow-up brain MRI. Information on coumarin use was obtained from automated pharmacy records. Coumarin users were monitored, and INR values were measured in consecutive visits. Presence and location of microbleeds were rated on brain MRI. We investigated the association of coumarin use with microbleeds using multivariable logistic regression.

Results—Overall, 8.6% had used coumarin anticoagulants before the first MRI and 5.9% before follow-up MRI. The prevalence of microbleeds was 19.4%, and the incidence was 6.9% during a mean follow-up of 3.9 years (SD, 0.5). Compared with never users, coumarin users had a higher prevalence of deep or infratentorial microbleeds and a higher incidence of any microbleeds, although statistical significance was not reached in the latter. A higher maximum INR was associated with deep or infratentorial microbleeds. Among coumarin users, a greater variability in INR was associated with a higher prevalence of microbleeds.

Conclusions—Coumarin use is associated with microbleeds. Associations were strongest for people with greater variability in INR. (Stroke. 2014;45:3436-3439.)

Key Words: anticoagulants cerebral small vessel disease epidemiology magnetic resonance imaging

Oral coumarin anticoagulants are widely used to treat patients with (risk of) thromboembolic diseases. Bleeding is a serious adverse effect of all oral anticoagulants, and intracerebral hemorrhages are among the most feared complications because of high morbidity and mortality rates.

Analogous to the increased risk of intracerebral hemorrhage, it is conceivable that oral coumarin anticoagulants also increase the frequency of smaller, subclinical hemorrhages. These so-called cerebral microbleeds are recognized as hypointense foci on brain MRI and are thought to represent hemosiderin depositions.

In the population-based Rotterdam Study we investigated, first, whether coumarin users had a higher prevalence and incidence of microbleeds compared with never users. Second, we studied whether microbleeds were more frequent in participants with a higher maximum international normalized ratio (INR) value. Third, among coumarin users, we studied whether variability in INR was associated with microbleed presence.

Methods

A detailed description of the Methods can be found in the online-only Data Supplement. The study was conducted within the population-based Rotterdam Study. Data on coumarin use were available in 4945 participants with a baseline MRI and in 3069 participants with follow-up MRI. We extracted the highest measured INR value before baseline brain MRI, as well as INR values measured in ≤10 consecutive visits after initiation of treatment to calculate INR variability. Microbleeds were rated on a T2*-weighted gradient-recalled echo sequence.

Logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs). First, we investigated the association between coumarin use and microbleeds after adjusting for age, sex, and cardiovascular risk factors. Second, we investigated the relation between maximum INR values and microbleed presence cross-sectionally, after adjusting for age, sex, and duration of coumarin use.
We categorized participants who used coumarin anticoagulants into groups of maximum INR values 1 to 4 (including 4); 4 to 6 (including 6); >6, depending on their highest measured INR, and compared them with a reference category of never users. Third, we investigated the association of variability in INR with the presence of microbleeds in coumarin users, after adjusting for age, sex, and duration of coumarin use. We calculated tertiles of variability in INR and compared highest with lowest tertiles.

**Results**

A total of 427 (8.6%) participants had used oral coumarin anticoagulants at some time before the first MRI. One or more microbleeds were seen on the baseline MRI scans of 957 (19.4%) participants (median number of microbleeds 1 [range, 1–111], 91% had ≤6 microbleeds). Of 3069 participants with follow-up MRI 181 (5.9%) participants had used coumarin anticoagulant drugs at some time before the second MRI scan. The cumulative incidence of microbleeds was 6.9% during a mean follow-up of 3.9 years (SD, 0.5; Table I in the online-only Data Supplement).

Participants who used coumarin anticoagulants had a higher prevalence of deep or infratentorial microbleeds (with or without lobar microbleeds) compared with never users (age and sex-adjusted OR for deep or infratentorial microbleeds 1.70; 95% CI, 1.24–2.34; Table). Although statistical significance was not reached, it seemed that compared with never users, coumarin users were at increased risk of developing new microbleeds (OR for any microbleeds, 1.44; 95% CI, 0.89–2.32). Associations remained similar after additional adjustments for cardiovascular risk factors. After taking into account the indication for coumarin use, we still found an association between coumarin anticoagulants and prevalent deep or infratentorial microbleeds (Table II in the online-only Data Supplement). In a post hoc analysis, we found a higher frequency of both strictly deep or infratentorial (age and sex-adjusted OR, 1.66; 95% CI, 1.06–2.60) and mixed microbleeds (deep or infratentorial with lobar microbleeds; OR, 1.71; 95% CI, 1.14–2.58) in coumarin users compared with never users.

Excluding participants who had used other antithrombotic agents besides coumarin anticoagulants did not change the results meaningfully (OR for prevalent deep or infratentorial microbleeds, 2.03; 95% CI, 1.23–3.36). Finally, excluding participants with infarcts on MRI did not alter the results (OR for prevalent deep or infratentorial microbleeds, 1.93; 95% CI, 1.32–2.82).

Deep or infratentorial microbleeds seemed more frequent in participants with a higher maximum INR value when compared with never users (linear trend tests across INR categories for deep or infratentorial microbleeds  P value=0.073; Figure 1).

Within the group of oral coumarin anticoagulant users, those within the highest tertile of variability in INR values

| Table. Use of Coumarin Anticoagulants and Microbleeds |
|----------------|-----------------|-----------------|-----------------|
|               | n/N             | Any Microbleeds  | Strictly Lobar  | Deep or Infratentorial |
|               |                 | (Yes vs No)      | Microbleeds     | Microbleeds           |
|               |                 | n/N              | (Yes vs No)     | n/N                |
| Prevalent microbleeds |      |                  |                  |                    |
| Model 1       |                  |                  |                  |                    |
| Never use     | 819/4518        | Reference        | 555/4254        | Reference            |
| Ever use      | 138/427         | 1.29 (1.02–1.62)*| 74/363          | 1.07 (0.80–1.42)     |
|               |                  |                  |                  |                    |
| Model 2       |                  |                  |                  |                    |
| Never use     | 791/4384        | Reference        | 535/4128        | Reference            |
| Ever use      | 134/412         | 1.25 (0.98–1.59) | 72/350          | 1.06 (0.79–1.42)     |
| Model 3       |                  |                  |                  |                    |
| Never use     | 667/3649        | Reference        | 453/3435        | Reference            |
| Ever use      | 120/345         | 1.33 (1.03–1.72)*| 67/292          | 1.18 (0.86–1.60)     |
| Incident microbleeds |          |                  |                  |                    |
| Model 1       |                  |                  |                  |                    |
| Never use     | 189/2888        | Reference        | 136/2835        | Reference            |
| Ever use      | 24/181          | 1.44 (0.89–2.32) | 14/171          | 1.25 (0.69–2.27)     |
| Model 2       |                  |                  |                  |                    |
| Never use     | 181/2812        | Reference        | 129/2760        | Reference            |
| Ever use      | 23/174          | 1.54 (0.94–2.54) | 13/164          | 1.34 (0.72–2.50)     |
| Model 3       |                  |                  |                  |                    |
| Never use     | 145/2346        | Reference        | 102/2303        | Reference            |
| Ever use      | 19/134          | 1.67 (0.96–2.89) | 11/126          | 1.44 (0.73–2.85)     |

Values represent estimated odds ratios (95% confidence interval) for prevalent and incident microbleeds in ever users vs never users of coumarin anticoagulants. Model 1: age, sex adjusted; model 2: age, sex, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol, smoking, diabetes mellitus, lipid-lowering, and antihypertensive medication adjusted (complete case analysis); and model 3: age, sex, total cholesterol, lipid-lowering medication, and apolipoprotein E ε4 carrierhip adjusted (complete case analysis). n/N indicates number of microbleed cases per exposure category/total study population within the exposure category. *P value <0.05.
after initiation of coumarin anticoagulants had a higher prevalence of deep or infratentorial microbleeds compared with those within the lowest tertile of variability in INR values (linear trend test across tertiles for deep or infratentorial microbleeds \( P \) value=0.048; Table III in the online-only Data Supplement). A greater variability in INR was associated with deep or infratentorial microbleeds, particularly for the first 5 measurements (Figure 2).

**Discussion**

In a large sample of people from the general population, we found that compared with never users, users of oral coumarin anticoagulants had more deep or infratentorial cerebral microbleeds on MRI and seemed to have an increased risk of developing new microbleeds. In addition, a greater variability in INR shortly after the initiation of coumarins was associated with the presence of deep or infratentorial microbleeds.

Strengths of our study are its population-based design, which increases generalizability, and the availability of longitudinal data, which offers insight into temporality of associations. Some methodological considerations need to be addressed. Imaging does not provide information on the date that cerebral microbleeds developed, and therefore it is possible that microbleeds may have occurred before the use of anticoagulant drugs. Also, confounding by indication may pose a problem in our observational study, as anticoagulants are prescribed more often to people with or at increased risk of cardiovascular disease, which in turn is related to cerebral microbleeds, especially deep or infratentorial microbleeds.\(^5\)\(^,\)\(^11\)

We tried to minimize confounding of our results in several ways. First, we adjusted for important cardiovascular risk factors. Note that the number of incident microbleeds cases was small, and results from multivariate analyses should be interpreted with caution. Second, we excluded participants with infarcts on MRI. Third, we took into account the indication of anticoagulant drug use. Fourth, we used variability in INR as a measurement less prone to confounding by indication, as this measure does not depend on the target INR but on whether the INR, regardless of its value, was stable across consecutive measurements.\(^8\)

Our study specifically focused on the relationship between coumarin anticoagulants and microbleeds, and we acknowledge that our findings may not be generalizable to populations using noncoumarin oral anticoagulants. As a final limitation we would like to mention that we did not study clinical events and thus cannot comment on the risk of anticoagulant-related major bleeding complications.

Our finding that coumarin anticoagulant users had a higher prevalence of microbleeds is in line with previous studies in ischemic or hemorrhagic stroke patients.\(^1\)\(^2\)\(^,\)\(^13\) Compared with these clinical reports, our study now provides additional insight into the subclinical bleeding complications of oral coumarin anticoagulants in stroke-free persons. We also showed that the use of coumarin anticoagulants seemed to increase the risk of developing new microbleeds. Microbleed development...
is thought to result from leakage of blood through the walls of small brain vessels that are damaged by either cerebral amyloid angiopathy or hypertensive arteriosclerosis. It has been hypothesized that this process can be halted by adequate hemostatic mechanisms, and the use of anticoagulants inhibits this mechanism. Thus anticoagulant drug use may serve as a catalyst in the presence of cerebral amyloid angiopathy or hypertensive arteriopathy to expand the number of microbleeds.

To date, it remains inconclusive whether anticoagulant drug use associates differently with microbleeds or intracerebral hemorrhage at various sites in the brain. We found that the association of coumarin use and microbleeds was primarily driven by the presence of deep or infratentorial microbleeds. This is in contrast to the majority of clinical studies that often found an association with lobar microbleeds. It should be noted that although lobar microbleeds have mainly been implicated in cerebral amyloid angiopathy and deep microbleeds in hypertensive arteriopathy, both types of pathologies may coexist and cause for a more severe mixed pathology. In our study, participants categorized as deep or infratentorial were allowed to also have microbleeds in lobar brain regions. Therefore, this group was more likely to have multiple microbleeds and potentially also mixed pathology, which could explain why associations were strongest for participants with deep or infratentorial microbleeds in our study.

Lack of statistical power is the most likely reason why we did not find a significant association between coumarin use and incident microbleeds. Nevertheless, our longitudinal analyses suggested an association between anticoagulant drug use and incident lobar microbleeds, which further supports the idea that the associations presented are not merely a reflection of confounding by indication.

Among oral coumarin anticoagulant users, the intensity of anticoagulation was shown to be a strong risk factor for bleeding complications. Regardless of the INR values, microbleeds were more frequently found in people with a greater variability in INR, particularly in the early phase after anticoagulant therapy initiation. A more vigilant monitoring of INR values and dosage requirements may become beneficial if future longitudinal studies show that microbleeds are indeed precursors of major intracerebral hemorrhage.

In conclusion, we found that oral coumarin anticoagulant use is associated with cerebral microbleeds. This association was particularly present for people with higher INR values and greater variability in INR.

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Dr Vernooij received a research fellowship from the Erasmus MC.

Disclosures
None.

References
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/11/3436

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/10/14/STROKEAHA.114.007112.DC1
SUPPLEMENTAL MATERIAL

Supplemental Methods

Participants
The study was conducted within the Rotterdam Study, a large population-based cohort study.1 Between 2005 and 2011, 6,367 participants were invited to undergo a baseline brain MRI-scan.2 In total 5,735 non-demented participants were eligible to take part in the study, and 5,074 actually participated. Data on 4,945 participants were available for cross-sectional analyses, after excluding incomplete scans (N=72) or scan of inadequate quality (N=57). Of those, 3,069 participants had complete follow-up MRI examinations, and were used in longitudinal analyses on incident microbleeds.

Oral anticoagulant drug use
Approximately 99% of participants were registered with one or more of seven pharmacies serving the study area. Complete automated records of all outpatient filled prescriptions were available for these participants from January 1991 onwards. Information on prescription included the product name, international non-proprietary name, anatomical therapeutic chemical (ATC) code, total number of delivered units, prescribed daily number of units, date of delivery, and drug dosage. The oral anticoagulants under study were coumarins (ATC code B01AA04 acenocoumarol, and B01AA07 phenprocoumon). Other antithrombotic medications of which the use was recorded were heparins (B01AB) and platelet aggregation inhibitors (B01AC). Overall, 427 participants had used coumarin anticoagulants at some time before baseline MRI, of whom 147 for the indication atrial fibrillation, 207 for the treatment or prophylaxis of deep venous thrombosis/pulmonary embolism, 24 for peripheral arterial occlusive disease, 47 for cardiac diseases (including coronary heart disease, heart failure, and valvular dysfunction), 1 person because of factor V Leiden mutation, and 1 person for antiphospholipid syndrome.

INR
Prothrombin times were monitored by a regional anticoagulant clinic (Star Medical Diagnostic Center) every 1-6 weeks, depending on target levels and stability of INR values. For each participant we extracted the highest measured INR value before baseline brain MRI, as well as INR values measured in up to 10 consecutive visits after initiation of treatment. The formula for variance growth rate as described by Fihn et al3 was applied to calculate INR variability from single INR values measured in two consecutive visits (i.e., the variability was calculated for INR measured at visit 1 and 2, visit 2 and 3, et cetera). A higher variance growth rate indicates greater fluctuations in INR values across consecutive measurements, irrespective of the target INR.4

Microbleed rating
All participants were scanned on the same 1.5-Tesla MRI scanner (GE,), using a multisequence protocol that included a T1-weighted, proton density-weighted and fluid-attenuated inversion recovery sequence.2 For microbleed detection we used a T2*-weighted gradient-recalled echo sequence (T2*GRE),5 optimized to increase the conspicuity of cerebral microbleeds. Microbleeds, defined as focal areas of low signal intensity on T2*GRE, were scored on presence, number, and location by 1 of 5 trained raters, using a protocol that was defined at the baseline of the study with good interobserver and intraobserver reliability.5 All baseline and follow-up scans that were rated positive for microbleeds were included in a side-
by-side comparison blinded to the time-point of the scans to assess the final number and location of microbleeds in each scan.

**Infarcts on MRI**
The presence of infarcts, i.e., lacunes, subcortical and cortical infarcts, was rated on MRI as described before.5

**Assessment of cardiovascular risk factors**
We considered various cardiovascular risk factors as potential confounders, namely blood pressure, serum total and high-density lipoprotein (HDL) cholesterol, smoking (‘ever’ versus ‘never’), diabetes mellitus (fasting glucose levels ≥7.0 mmol/L, ≥11.1 mmol/L if fasting samples were unavailable, or the use of any glucose-lowering medication), use of lipid-lowering and blood-pressure-lowering medication (assessed by interviews during home visits), and **Apolipoprotein E (APOE)** genotyping which was performed on coded genomic DNA samples.

**Statistical analysis**
Participants were grouped into ever versus never-users of coumarin anticoagulants. Microbleed presence was investigated dichotomously (present versus absent) and by location. We categorized microbleeds as strictly lobar (presumed to reflect cerebral amyloid angiopathy [CAA]),5 or as deep or infratentorial microbleeds irrespective of the presence of any lobar microbleeds (presumed to reflect hypertensive arteriopathy).5 Logistic regression was used in all analyses to obtain odds ratios (OR) and 95% confidence intervals (CI).

In the first analysis, we used three models to study the relation between coumarin anticoagulant use, the prevalence of microbleeds, and the risk of microbleeds. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for cardiovascular risk factors associated with deep or infratentorial microbleeds, namely systolic and diastolic blood pressures, serum total and HDL cholesterol, smoking, diabetes mellitus, lipid-lowering and antihypertensive medication. Model 3 was adjusted for age, sex, total cholesterol, lipid-lowering medication and **APOE** genotype, as **APOE** ε4 carriership is a strong risk factor for lobar microbleeds and because of the role of **APOE** in lipid metabolism. To address potential confounding by indication in our study we repeated the analyses described above in model 1, 2, and 3 whilst also adjusting for the indication of coumarin anticoagulant drug use. Sensitivity analyses were done excluding participants who had used other antithrombotic agents (e.g., heparin, aspirin) to demonstrate the pure association of oral coumarin anticoagulants and microbleeds. Also, to further reduce potential confounding by indication, all analyses were repeated after excluding participants with infarcts on MRI.

In the second analysis, we investigated the relation between maximum INR values and microbleed presence cross-sectionally after adjustments for age sex, and duration of coumarin use. To this end, we categorized participants who used coumarin anticoagulants into groups of maximum INR values 1-4 (including 4); 4-6 (including 6); >6, depending on their highest measured INR, and compared them to a reference category of never-users (assumed INR value of 1). The cut-off points were chosen pre-hoc using Dutch guidelines for managing anticoagulant therapy. The cut-off of 4 was chosen based on what was considered to be the upper therapeutic range for the most common indications when using anticoagulants, and INR of 6 was chosen because based on previous literature an increased risk of ICH was particularly shown when INR exceeded this level.6 The third analysis was restricted to participants who had used coumarin anticoagulants. We investigated the association of variability in INR with the presence of microbleeds after
adjusting for age, sex, and duration of coumarin use. We calculated tertiles of variability in INR and compared highest to the lowest tertiles.

Analyses were done using the statistical software package IBM SPSS Statistics version 20.0 using an $\alpha$-value of 0.05.
## Supplemental Tables

### Supplementary Table I. Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>People with baseline MRI (N=4,945)</th>
<th>People with follow-up MRI (N=3,069)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64.0 (11.0)</td>
<td>59.7 (8.1)</td>
</tr>
<tr>
<td>Women</td>
<td>2724 (55.1)</td>
<td>1657 (54.0)</td>
</tr>
<tr>
<td>Ever use of coumarin anticoagulants before MRI</td>
<td>427 (8.6)</td>
<td>181 (5.9)</td>
</tr>
<tr>
<td><strong>Exclusive use of coumarin anticoagulants</strong></td>
<td><strong>186 (3.8)</strong></td>
<td><strong>89 (2.9)</strong></td>
</tr>
<tr>
<td>INR values at check-up visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always 1-4</td>
<td>151 (3.1)</td>
<td>60 (2.0)</td>
</tr>
<tr>
<td>At least once 4-6</td>
<td>210 (4.2)</td>
<td>94 (3.1)</td>
</tr>
<tr>
<td>At least once &gt;6</td>
<td>66 (1.3)</td>
<td>27 (0.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>138.9 (21.2)</td>
<td>134.9 (19.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>82.2 (10.9)</td>
<td>81.9 (10.7)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.5 (1.1)</td>
<td>5.6 (1.0)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mmol/L</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>3436 (69.5)</td>
<td>2125 (69.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>433 (8.8)</td>
<td>224 (7.3)</td>
</tr>
<tr>
<td>Lipid-lowering medication use</td>
<td>1185 (24.0)</td>
<td>653 (21.3)</td>
</tr>
<tr>
<td>Antihypertensive medication use</td>
<td>1696 (34.3)</td>
<td>816 (26.6)</td>
</tr>
<tr>
<td><strong>Apolipoprotein E e4 carriership</strong></td>
<td><strong>1314 (26.6)</strong></td>
<td><strong>801 (26.1)</strong></td>
</tr>
<tr>
<td>Lacunar infarcts</td>
<td>368 (7.4)</td>
<td>150 (4.9)</td>
</tr>
<tr>
<td>Subcortical infarcts†</td>
<td>9 (0.2)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Cortical infarcts</td>
<td>165 (3.3)</td>
<td>67 (2.2)</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean (standard deviation) and categorical variables as number (percentage). All values presented are baseline values.

*Participants who used other antithrombotic agents (i.e., subcutaneous anticoagulants and platelet aggregation inhibitors) were excluded.

†Subcortical infarcts were defined as lacunar infarcts ≥ 15mm in size.\(^5\)

INR= international normalized ratio.

The following variables had missing data in the analysis of people with baseline MRI: blood pressures (N=21), total cholesterol (N=74), high-density lipoprotein cholesterol (N=76), smoking (N=26), diabetes mellitus (N=81), lipid-lowering and antihypertensive medication (N=42), Apolipoprotein E genotype (N=347).

The following variables had missing data in the analysis of people with follow-up MRI: blood pressures (N=12), total (N=33) and high-density lipoprotein cholesterol (N=35), smoking (N=9), diabetes mellitus (N=58), lipid-lowering and antihypertensive medication (N=31), Apolipoprotein E genotype (N=206).
### Supplementary Table II. Use of coumarin anticoagulants and microbleeds, adjusted for indication of anticoagulant use.

<table>
<thead>
<tr>
<th></th>
<th>Any microbleeds (yes vs. no)</th>
<th>Prevalent microbleeds</th>
<th>Strictly lobar microbleeds (yes vs. no)</th>
<th>Deep or infratentorial microbleeds (yes vs. no)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>n/N</td>
<td>n/N</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never use</td>
<td>819/4518</td>
<td>Reference</td>
<td>555/4254</td>
<td>Reference</td>
</tr>
<tr>
<td>Ever use</td>
<td>138/427</td>
<td>1.51 (0.92-2.50)</td>
<td>74/363</td>
<td>1.10 (0.58-2.09)</td>
</tr>
<tr>
<td>Ever use</td>
<td>134/412</td>
<td>1.38 (0.82-2.33)</td>
<td>72/350</td>
<td>1.00 (0.51-1.97)</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never use</td>
<td>791/4384</td>
<td>Reference</td>
<td>535/4128</td>
<td>Reference</td>
</tr>
<tr>
<td>Ever use</td>
<td>134/412</td>
<td>1.38 (0.82-2.33)</td>
<td>72/350</td>
<td>1.00 (0.51-1.97)</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never use</td>
<td>667/3649</td>
<td>Reference</td>
<td>453/3435</td>
<td>Reference</td>
</tr>
<tr>
<td>Ever use</td>
<td>120/345</td>
<td>1.77 (1.03-3.04)*</td>
<td>67/292</td>
<td>1.32 (0.67-2.59)</td>
</tr>
</tbody>
</table>

Model 1: age, sex, and indication of anticoagulant drug use adjusted.
Model 2: age, sex, systolic and diastolic blood pressure, total and high-density lipoprotein cholesterol, smoking, diabetes mellitus, lipid-lowering and antihypertensive medication, and indication of anticoagulant drug use adjusted. (Complete-case analysis).
Model 3: age, sex, total cholesterol, lipid-lowering medication, and *apolipoprotein E* ε4 carriehship, and indication of anticoagulant drug use adjusted. (Complete-case analysis).

Values represent estimated odds ratios (95% confidence interval) for microbleeds in ever versus never-users of coumarin anticoagulants.

*Indicates p-value < 0.05. n/N= number of microbleed cases per exposure category/ total study population within the exposure category.
Supplementary Table III. Variability in INR and microbleed presence.

<table>
<thead>
<tr>
<th></th>
<th>Any microbleeds (yes vs. no)</th>
<th>Strictly lobar microbleeds (yes vs. no)</th>
<th>Deep or infratentorial microbleeds (yes vs. no)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>n/N</td>
</tr>
<tr>
<td>Prevalent microbleeds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; tertile</td>
<td>44/142 Reference</td>
<td>27/125 Reference</td>
<td>17/115 Reference</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; tertile</td>
<td>43/144 0.98 (0.58-1.66)</td>
<td>25/126 0.92 (0.49-1.74)</td>
<td>18/119 1.08 (0.51-2.26)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; tertile</td>
<td>51/140 1.40 (0.84-2.34)</td>
<td>22/111 0.97 (0.51-1.85)</td>
<td>29/118 1.95 (0.99-3.86)</td>
</tr>
</tbody>
</table>

Values represent age, sex, and duration of coumarin use adjusted odds ratios (95% confidence interval) for microbleed presence in relation to tertiles of variability in INR among ever-users of oral coumarin anticoagulants. The 1<sup>st</sup> tertile consists of coumarin anticoagulant users with the lowest variability in INR. INR= international standardized ratio. n/N= number of people using coumarin anticoagulants and had microbleeds/total number of people in the tertile.
Supplemental References